REMARKS

The following remarks explain the basis for the amendments and address certain comments and rejections mentioned in the Office Action, Paper No. 14, dated January 28, 2003.

Discussion of the Claims

Claim 1 covers a process of the invention for isolating nucleic acids, wherein the nucleic acids are immobilized to, released from, and removed from one and the same side of a non-siliceous surface. Claim 51 covers an embodiment of the invention wherein the surface is a membrane. Applicants have amended both Claims 1 and 51 to expressly state a feature of the that claimed process, i.e., that "the nucleic acids do not penetrate to or make contact with the other opposing side of" the non-siliceous surface (in Claim 1), or, the membrane (in Claim 51). Applicants have also amended Claim 51 in order to recite steps of the process with affirmative language (e.g., "immobilizing", "releasing", "collecting"); to specifically incorporate the preferred embodiment of original Claim 52, now canceled, i.e., wherein the membrane comprises any of a group of specified (non-siliceous) materials; and to recite that the membrane may be hydrophilic, hydrophobic, hydrophilisized, or hydrophobisized. The amendment to Claim 51 is also consistent with the language of dependent Claims 53-55. In view of the amendment to Claim 51 and the cancellation of Claim 52, Applicants have also adjusted the language and dependencies of Claims 53 and 58. Applicants have also added new dependent Claim 69, which specifies additional steps that may be employed in carrying out the process according to Claim 51, as amended herein. Support for the amendments is found in Summary of the Invention, drawings, and actual working Examples of the specification (see, e.g., p. 5, lines 5-16; p. 8, line 10-p. 9, line 20 (membranes); p. 11, lines 7-13; Figures 2-4; Examples 1-19, pp. 16-39; and original Claim 52, of the specification). Accordingly, the amendments add no new matter.

Applicants also have amended Claim 41 to specify only the broadest size range for diameters of pores in a membrane useful in the claimed invention, i.e., "0.001 to 50 micrometers". The other two smaller size ranges of original Claim 41, i.e., 0.01 to 20 micrometers and 0.05 to 10 micrometers, are now covered in new Claims 67 and 68, respectively, that depend from Claim 41. Accordingly, the amendment and new Claims 67 and

68 add no new matter, but are made to better conform the claims to claim practice in the US Patent Office.

Applicants have also added new Claim 69 to expressly cover the process of Claim 51, as amended herein, comprising the particular steps of mixing the nucleic acids with an immobilization buffer, charging the nucleic acids with the immobilization buffer onto the membrane, optionally, washing the nucleic acids immobilized on the membrane, and drawing the unbound fluid components of the immobilization buffer or wash buffer through the membrane. Support for new Claim 69 is found throughout the specification (see, e.g., p. 4, lines 11-18; p. 5, lines 7-11; p. 10, lines 13-29; p. 11, lines 7-13; and Examples 1-19, pp. 16-39, of the specification). Accordingly, new Claim 69 adds no new matter.

Finally, Applicants have added new dependent Claims 70-75, to cover the process according to Claim 51 or Claim 69, using particular immobilization buffers and conditions. New Claim 70 covers the process according to Claim 69, wherein the immobilization buffer includes alkaline or alkaline earth metals with mineral acids. Support for new Claim 70 is found in original Claim 10. New Claim 71 covers the process according to Claim 69, wherein the immobilization buffer includes aqueous solutions of salts of monobasic or polybasic or polyfunctional organic acids with alkaline or alkaline earth metals. Support for new Claim 71 is found in original Claim 13. New Claim 72 covers the process according to Claim 69, wherein the immobilization buffer includes hydroxyl derivates or aliphatic or acyclic saturate or unsaturated hydrocarbons. Support for new Claim 72 is found in original Claim 18. New Claim 73 covers the process according to Claim 69, wherein the immobilization buffer is a phenol or polyphenol. Support for new Claim 73 is found in original Claim 22. New Claim 74 covers the process according to Claim 51 or Claim 69, wherein a chaotropic agent is used in the immobilization of the nucleic acids. Support for new Claim 74 is found in original Claim 44. New Claim 75 covers the process according to Claim 51 or Claim 69, wherein the immobilization of the nucleic acids takes place at a pH of from 3 to 11. Support for new Claim 75 is found in original Claim 58. Additional support for the various immobilization buffers and conditions recited in new Claims 70-75 is found elsewhere in the specification (see, e.g., p. 6, line 29-p. 8, line 4; Examples 1-19, pp. 16-39, of the specification).

Entry of the amendments is respectfully requested.

Response to Rejection Under 35 USC § 112, first paragraph

In the Office Action (Paper No. 14), The Examiner rejected Claims 1-5, 9-22, 24-41, 44-50, and 59-64 under 35 USC § 112, first paragraph, as containing:

> "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 4 and 5 have been amended to recite that surface is 'non-silicious'. No support for the exclusion of the species of 'siliceous' surfaces from the genus of claimed surfaces has been found in the instant originally filed claims or specification. No citation or argument has been provided in the amendment of Paper [No.] 13 to support the amendment of claims 1, 4 and 5 reciting a surface which is 'non-silicious". Therefore, the term 'non-silicious' constitutes new matter." (section 11, pp. 3-4, of the Office Action, Paper No. 14).

For the reasons indicated below, Applicants respectfully traverse the rejection.

Applicants first note that the term "non-siliceous" in Applicants' claims is properly spelled and that the term is supported by the specification and understood by persons skilled in this art who read Applicants' specification.

The specific term "non-siliceous" need not appear in the specification in order to be used in the claims, because the sense of the term "non-siliceous" is conveyed by the disclosure as a whole. It has been long settled that a patent specification need not describe the claimed invention using the exact terms used in the claims, i.e., there is no requirement for the claim terminology to appear *in haec verba* in the disclosure. As recently noted by the Court of Appeals for the Federal Circuit in *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 64 USPQ2d 1945 (Fed. Cir. 2002):

> "In order to comply with the written description requirement, the specification 'need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed.' [citations omitted]
>
> * * *
>
> "Here, the invention involves heating a mass of thermoplastic material that lacks an identifiable form. ***That invention is***

> ***described in the specification, albeit not in haec verba. It is also clear what the invention is not.*** It does not involve heating a thermoplastic mass having an identifiable form or shape." (*All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 USPQ2d 1945, 1948 (Fed. Cir. 2002) (emphasis added)

See, also, *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989) and *In re Smith*, 481 F.2d 910, 178 USPQ 620 (CCPA 1973).

Respectfully, there appears to be no legal basis for the Examiner's rejection. Applicants have the right to claim any and all inventions disclosed in their specification. Siliceous and non-siliceous surfaces that may be employed in the invention are clearly described throughout the specification (see, e.g., p. 8, line 15-p. 9, line 20; Examples 1-19 at pp. 16-38, of the specification), and persons skilled in this art who read the specification would readily distinguish between these two well-known categories of surfaces commonly employed in nucleic acid biochemical protocols. Thus, Applicants have amended the claims in this application to clearly and specifically focus coverage on processes of the invention that employ what persons skilled in this art would readily recognize as "non-siliceous" surfaces. The law does not require more of the written description (see, above).

In addition, contrary to the Examiner's view, Applicants' specification provides a number of statements and examples that indicate or illustrate to persons skilled in this art that non-siliceous surfaces are particularly preferred over siliceous surfaces for use in particular embodiments of the invention. For example, the specification notes:

> "Less preferred, on the other hand, are fleeces such as *silica* fleeces, . . ." (p. 11, line 30, of the specification; emphasis added).

Example 1 (p. 16, line 10-p. 18, line 10, of the specification) compares yields of total RNA from lysed HeLa cells applied to and removed from one and the same side of nylon membranes or of a silica membrane. As noted in an analysis of the results of Example 1:

> "The results of the two isolations with hydrophobic nylon membranes (Nos. 1 and 2) are shown in Table 1, compared with experiments in which on the one hand a hydrophilic nylon (Nyaflo) (No.3) and *a silica membrane* (No. 4) were used. The values reported in the table provide convincing support for the impressive isolation yield and separation effect of the materials used in

> accordance with the invention. They also show that *silica* gel-fleece produces clearly less yield, which can be attributed to its fleecelike structure and the ensuing absorption of a large portion of the eluted buffer." (p. 17, lines12-18, of the specification; emphasis added)

And later in Example 1:

> "Fig. 6 provides convincing evidence that when a *silica* membrane is used, no measurable proportion of the total RNA can be isolated." (p. 18, lines 9-10, of the specification; emphasis added)

Example 1 of the specification is then followed by Examples 2-16 that provide a variety of studies and demonstrations of the claimed process to isolate nucleic acids by employing various surfaces that are clearly non-siliceous, e.g., hydrophobic forms of nylon, polyesters, polyether sulfone, acryl copolymers, polytetrafluor ethylene, and polyvinylidene fluoride (see, e.g., Table 3, pp. 21-22; Table 4, p. 23, of the specification). Examples 17-19 provide other studies and examples of carrying out the claimed process to isolate nucleic acids employing various hydrophilic, non-siliceous surfaces, e.g., hydrophilic forms of polyether sulfone, polyesters, polyamide, polyvinylidene fluoride, polycarbonate, and polypropylene fleece (see, e.g., Table 13, p. 37; Table 14, p. 39, of the specification). After the many demonstrations and studies in these subsequent Examples of how to achieve excellent yields of nucleic acids using non-siliceous surfaces, a final statement is provided in Example 19 that, again, expresses a clear preference for non-siliceous surfaces over siliceous surfaces in the claimed invention:

> "By using a *silica* membrane, no measurable amount of total RNA can be isolated if the eluate is taken from the membrane by drawing it off from the top." (p. 38, lines 17-18, of the specification; emphasis added)

Applicants submit that the above examples from the specification are more than sufficient to provide persons skilled in this art who read Applicants' specification with a teaching of a clear preference for practicing the invention using a non-siliceous surface over a siliceous surface. Accordingly, the specification clearly supports Applicants' claims to the preferred embodiment of the invention using non-siliceous surfaces.

In view of the above comments and examples, Applicants respectfully submit that the specification clearly supports the claims and that the rejection under 35 USC § 112, first paragraph, is improper. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

Response to Rejection Under 35 USC § 102

In the Office Action, the Examiner rejected Claims 1-5, 9-15, 18-21, 24-26, 28-32, 36, 39-41, 50-52, 55, 58-60, and 62 as anticipated by US Patent No. 5,234,824 ("Mullis"). In particular, the Examiner stated:

> "Mullis teaches at the abstract, the summary and example 6, a process for isolating nucleic acids comprising charging a non-silicious surface (filter) with nucleic acid from the top of the surface. The nucleic acid is immobilized (trapped) on the surface of the filter, and released (eluted) off of the surface of the filter on the same side (top side) of the filter. The nucleic acid may be washed with a buffer solution. The buffer may contain metal ion (salt), a chaotropic agent (ammonium sulfate) or an alcohol. The filter is hydrophilic. The releasing solution may be water or a buffer solution which may contain a metal ion (salt), a chaotropic agent (ammonium sulfate) and an alcohol. The process may be done in a multiwell plate." (section 13, p. 4, of the Office Action)

For the reasons provided below, Applicants respectfully traverse the rejections.

For anticipation under 35 U.S.C. § 102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in § 2131 of the Manual of Patent Examining Procedure (MPEP):

> **"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**
>
> " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

As noted above, Applicants' claims, as amended herein, clearly cover a process for isolating nucleic acids that comprises immobilizing nucleic acids on one side of a non-siliceous surface, releasing the immobilized nucleic acids from the non-siliceous surface, and removing the released nucleic acids from the same side of the non-siliceous surface on which the nucleic acids were immobilized, wherein the nucleic acids do not penetrate to or make contact with the other opposing side of the non-siliceous surface. Such steps and features of Applicants' invention are neither taught nor suggested by Mullis. Mullis expressly teaches a method that requires gentle lysis of blood cells and avoidance of high shear forces to permit sufficiently high molecular weight DNA to be released and trapped in a membrane filter and, further, that subsequent release of the DNA trapped on the filter is carried out by physically transferring the filter into a vessel, e.g., a tube or cell culture dish, immersing and shaking the filter in an elution buffer added to the vessel at elevated temperature (e.g., 37° - 100° C), and subsequently retrieving the DNA released into the elution solution in which the filter is immersed:

> "The present invention contemplates releasing the DNA trapped on the filter by *immersing the membrane filter in a sufficient amount of distilled water heated to about 100° C.*" (Summary of the Invention, col. 3, lines 36-39, of Mullis; emphasis added)

> "The most preferable method for releasing the high molecular weight purified DNA trapped on the filter *involves immersing the filter in an eluant which is heated to about 100° C.* As shown in Example 8, the washed *filters can be removed to a buffer containing magnesium in a tightly closed tube which is placed in a boiling water bath.*" (col. 6, lines 55-61, of Mullis; emphasis added)

> "The optimal method for releasing the high molecular weight DNA trapped on the filter, as shown in Example 9, involves *removing the washed filter to a solution* of distilled water in a tightly closed tube which is placed in a boiling water bath." (col. 6, lines 64-68, of Mullis; emphasis added)

> "The filters *were removed* from the vacuum manifold *and placed into 1 ml aliquots of an elution buffer* containing 80 mM Tris-HCl at pH 9.0, 20 mM ammonium sulfate, 10 mM magnesium chloride *in the shallow well of CostarTM (Cambridge, Ma.) plastic cell culture dishes.* The dishes were placed on a rotary shaker for

> several hours at 37° C, at which time they were discovered to have evaporated to dryness. After addition of 1 ml aliquots of water, the dishes were placed back into the shaker for 30 minutes and aliquots taken for analysis." (Example 3, col. 9, lines 55-64, of Mullis; emphasis added)
>
> "Filter membranes retaining trapped DNA were prepared as in Example 3. *The filters were removed from the apparatus and each placed in a shallow well of a Costar TM plastic cell culture dish, and treated with one milliliter of elution buffer* as described in Table 3. Elution was performed at 42° C, with gentle rocking on a thermostated rotary shaker for 15 minutes at which point the liquid was decanted and analyzed at 260 nM and 280 nM for the appearance of DNA." (Example 6, col. 12, lines 28-36, of Mullis; emphasis added).

Thus, as Examples 3 and 6 of Mullis illustrate, the method of Mullis involves a filter membrane that contains trapped DNA and that must be physically manipulated by immersing the filter membrane in a buffer solution in a vessel and shaking the filter in the vessel at elevated temperature above room temperature in order to obtain DNA from the filter membrane. It would be immediately evident to a person of ordinary skill in the art that immersing a filter containing DNA into an elution buffer in a vessel as described by Mullis will result in both sides of the filter necessarily being bathed with and contacting any DNA released from the filter. In contrast, Applicants' process does not involve a physical transfer and immersion of a non-siliceous surface containing immobilized nucleic acids to a bath for release and removal of the immobilized nucleic acids or any other manipulation that would permit both opposing sides of the non-siliceous surface to contact the nucleic acids. Furthermore, Applicants' claimed invention does not require that the release of nucleic acids from a non-siliceous surface must necessarily be carried out at an elevated temperature.

Moreover, the features of Applicants' invention are particularly advantageous in some settings. For example, in Applicants' process, buffers and other non-nucleic acid components that are applied to the one side of the non-siliceous surface containing immobilized nucleic acids may pass (e.g., by vacuum, absorption, or gravity) to the opposing second side, which can be considered a "waste side", of the non-siliceous surface (see, e.g., p. 11, lines 7-13; p. 15, lines 7-18, of the specification). Such a feature permits the "nucleic acid side" of the non-siliceous

surface to be used as a reaction area wherein the eluted nucleic acid may be subjected to one or more modification reactions, then re-immobilized for washing or separation from reaction reagents, and finally re-eluted for removal of the modified nucleic acids from the same side of the non-siliceous surface (see, e.g., p. 12, lines 5-12; of the specification; Claim 9). Such advantages and steps of Applicants' claimed process are neither taught nor suggested, nor even attainable, in the process of Mullis in which DNA is released from filters by immersing and shaking filters in a bath of elution buffer (see, excerpts, above).

The above comments and examples illustrate the clear differences in the method of Mullis and that of Applicants' claimed invention. Applicants submit that Mullis clearly fails to teach each and every element of Applicants' claims, and, thus, fails as a reference to anticipate Applicants' claims under 35 USC § 102. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Response to Rejections Under 35 USC § 103

In the Office Action, the Examiner rejected claims as obvious over Mullis, as the primary reference, in combination with one or more of US Patent No. 6,028,186 ("Tasset"), WO 97/08547 ("Su"), US Patent No. 5,869,073 ("Sawan"), EP 0 587 951 ("Raybuck"), and US Patent No. 5,728,531 ("Yamada"). Tasset is relied on by the Examiner as a teaching for the use of an elution buffer containing urea and phenol; Su, Sawan, and Raybuck are cited for use of particular membranes in nucleic acid isolation protocols; and Yamada is cited as a teaching for use of citric acid as immobilization and wash buffers in nucleic acid isolation protocols. For the reasons provided below, Applicants respectfully traverse the rejections.

Applicants first note that neither Mullis nor any of the additional documents mentioned above provides any suggestion or motivation to be combined as presented by the Examiner to provide Applicants' invention for isolating nucleic acids in which nucleic acids are immobilized on, released from, and removed from one and the same side of a non-siliceous surface, wherein the nucleic acids do not penetrate to or contact the other side of the non-siliceous surface. The patent law clearly forbids unmotivated combinations of references as hindsight reconstruction, so that rejections based on such combinations are improper. *See, In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). As there is no evidence of a motivation or teaching in Mullis or

in any of the other documents for any of the combinations presented in the Office Action, the combinations are clearly improper and cannot support a case of *prima facie* obviousness under 35 USC § 103.

Nevertheless, even if the documents are so combined, persons of ordinary skill in the art are still not provided with an example or even an appreciation of isolating nucleic acids according to Applicants' claimed invention. Again, none of Tasset, Su, Sawan, Raybuck or Yamada, with or without Mullis, describes Applicants' process for isolating nucleic acids in which nucleic acids are immobilized on, released from, and removed from one and the same side of a non-siliceous surface, wherein the nucleic acids do not penetrate to or contact the other side of the non-siliceous surface.

For example, the Examiner rejected Claims 1-5, 9-15, 18-22, 24-32, 36, 39-41, 44-52, 55, and 58-63 as obvious over Mullis in view of US Patent No. 6,028,186 ("Tasset"). The Examiner applied the primary reference Mullis as teaching Applicants' invention as in the rejection under 35 USC § 102, but further states:

> "Mullis did not teach that the process buffer may contain phenol or various chaotropic agents in claims 27 or 45 which may be in the immobilization buffer.
>
> "Tasset et al. teach at columns 19-20 the isolation of nucleic acids on a surface and the release of the nucleic acids from the surface where the *immobilization buffer, wash buffer* or elution buffer *may contain urea (one of the instant claimed chaotropic agents) and phenol.*
>
> "It would have been prima facie obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Mullis with Tasset et al. because each of Mullis and Tasset et al. teach a process for isolating nucleic acids comprising charging a non-silicious surface with nucleic acid from the top of the surface where the nucleic acid is immobilized on the surface of the filter, and released off of the same side of the surface. The teachings of Tasset et al. make obvious the modification of the method by using an immobilization buffer, wash buffer or elution buffer which may contain urea (one of the instant claimed chaotropic agents) and phenol." (section 15, pp. 6-7; of the Office Action, emphasis added)

As discussed above, the primary reference Mullis describes a process for obtaining genomic DNA by applying a lysate of blood cells to a filter membrane in a vacuum manifold apparatus, physically dismantling the apparatus to obtain the filter membrane to which genomic DNA has been applied, transferring the filter membrane to a cell culture dish, immersing the filter in an elution buffer in the culture dish, and incubating the culture dish on a rotatory shaker to elute the genomic DNA trapped in the filter membrane at elevated temperature (see, e.g., col. 9, lines 55-64; col. 10, lines 44-45; col. 12, lines 33-36, of Mullis). In contrast, Applicants' claimed process for isolating nucleic acids comprises immobilization, release, and removal of nucleic acids with respect to one and the same side of a non-siliceous surface wherein the nucleic acids do not penetrate to or contact the other opposing side of the non-siliceous surface. Clearly, Mullis fails to teach or suggest Applicants' claimed process.

Tasset does not cure the deficiencies of Mullis to make Applicants' claimed process obvious. Nowhere does Tasset describe Applicants' claimed process. The inventive feature of Applicants' claimed process does not reside solely in using an immobilization buffer comprising a strong chaotropic agent, such as urea (e.g., Claims 27, 45), or comprising a phenol (e.g., Claim 22; Example 13, p. 31, lines 5-15, of the specification). Notwithstanding this point, persons skilled in this art would recognize that, unlike Applicants' process, the process described in Tasset ***cannot*** employ an immobilization or wash buffer containing urea and/or phenol without destroying the binding ability of the molecules of interest to the filters. The reason for this prohibition is that Tasset describes use of the SELEX procedure (US Patent No. 5,270,163, "Gold", excerpts in Exhibit A) for synthesizing and selecting high affinity RNA ligands that bind a target protein (e.g., IFN-gamma in Tasset). The SELEX procedure employed in Tasset relies on a partitioning phenomenon that is well known in the field of molecular biology, i.e., under proper conditions certain protein/nucleic acid ligand *complexes* (e.g., certain protein/RNA ligand complexes in the SELEX procedure) will bind (partition to) nitrocellulose filters whereas free (undesired) nucleic acid (e.g., RNA not complexed with a protein target ligand in the SELEX procedure) is typically not retained on such filters and, therefore, is readily washed through or otherwise removed from such filters (see, e.g., col. 24, line 65-col. 25, line 21; col. 34, lines 19-30; col. 35, lines 26-31; col. 37, lines 38-43; of Gold in Exhibit A). In fact, "wash buffers" containing dilute urea (e.g., 0.5 M) may be used *to disrupt* weak binding of undesired

RNA/protein complexes in order to wash such undesired RNA and proteins through the filters, thereby decreasing background and increasing the stringency for desired complexes (see, e.g., col. 20, lines 35-42, of Tasset). The RNA in desired protein/RNA ligand complexes bound to nitrocellulose filters may then be *released* from such filters by immersing the filters in a bath of a phenol/7 M urea buffer at elevated temperature (see, e.g., col. 20, lines 42-48, of Tasset; col. 25, line 67-col. 26, line 20, of Gold in Exhibit A). Thus, immobilization buffers and/or wash buffers containing a chaotropic agent or other protein denaturant (e.g., phenol) as might be used in Applicants' invention to retain desired nucleic acids on a non-siliceous surface are clearly ***destructive*** to the goal of Tasset (or Gold) as such buffers would ***prevent*** retention of desired protein/RNA ligand complexes on nitrocellulose filters, and, thereby, prevent isolation of desired RNA species.

In contrast to Tasset, Applicants' process for isolating nucleic acids does not rely on the partitioning phenomenon of nucleic acid/protein ligand complexes described in Tasset and, to the contrary, is able to provide excellent yields using immobilization and wash buffers comprising the very denaturing compounds (see, e.g., Examples 1-19; of the specification) that would render the process described in Tasset (and Gold) inoperable. Clearly, Tasset does not teach or suggest use of immobilization and wash buffers according to Applicants' claimed invention and, thus, cannot cure the deficiencies of Mullis.

In view of the above explanation and Exhibit A, Applicants respectfully submit that the combination of Mullis with Tasset clearly does not provide a case of *prima facie* obviousness under 35 USC § 103. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also rejected Claims 1-5, 9-15, 18-22, 24-36, 39-41, 44-52, 55, and 58-63 as obvious over Mullis in combination with Tasset and WO 97/08547 ("Su"). The Examiner relied on Mullis and Tasset as in the earlier rejection and further applied Su because:

> "Mullis and Tasset et al. did not teach that the membrane may be *hydrophobic* (various types of *hydrophobic* membranes).
>
> "Su teach at the summary at pages 3-7, example 1 and claims 29-37 the use of *hydrophobic* membranes, and hydrophobized membranes in a method of binding and releasing nucleic acids from the surface of a membranes [sic] with immobilization buffers, washing buffers and releasing buffers containing ionic metal salts,

> organic acid salts, or hydroxyl derivatives of aliphatic hydrocarbons (alcohols). . . .
>
> "One of ordinary skill in the art would have been motivated to combine the teachings of Mullis, Tasset et al. and Su because Su at page 2, [sic] the desirable and beneficial use of the *hydrophobic* surfaces to improve the immobilization (section 16, pp. 7-8 of the Office Action; emphasis added)

Applicants respectfully traverse the rejection based on the comments below.

At the outset, Applicants note that Su describes the use of a matrix comprising a *hydrophilic*, not hydrophobic, organic polymer in a method and apparatus to isolate nucleic acids (see, Abstract, Summary at pp. 3-7, Example 1 (cellulose, e.g., from Whatman 3 MM paper), Claims 1-37, of Su). Thus, Su does not provide any literal support for the Examiner's reasoning.

Applicants refer to their comments above demonstrating the deficiencies of the combination of Mullis and Tasset as a basis for rejecting Applicants' claims as obvious. With respect to Su, even assuming, *arguendo*, that the Examiner meant to rely on Su as a reference for using a hydrophilic matrix to isolate nucleic acids, Su still fails at a more fundamental level to cure the deficiencies of Mullis and Tasset. The inventive feature of Applicants' invention does not rest in the fact that non-siliceous, hydrophilic or hydrophobic surfaces were discovered to operate in the method of the invention; Applicants have stated that examples of such materials are known and have been readily available from a variety of commercial sources for many years (see, Examples 1-19 of Applicants' specification). In Su, the hydrophilic solid matrix (processed from Whatman 3 MM filter paper) is employed in various standard formats, e.g., in a column, wherein nucleic acid eluted out of the bottom the column (see, Su at p. 9, lines 2-14; Examples 1-4), in a suspension or batch format (see, Su at p. 8, line 9-p. 9, line 1; Example 5), or coated on collectible particles (see, Su at Example 9). Using the matrix of Su involves exposing and contacting the entire surface of the matrix to nucleic acids, which is expressly ***not*** permitted in Applicants' invention (see, amendments to the claims, above). Nowhere does Su provide a description or appreciation for Applicants' process in which nucleic acid is immobilized on one side of a non-siliceous surface and also released and removed from one and the same side and wherein the nucleic acid does not penetrate to or contact the other side of the non-siliceous surface. Su only refers to recovering nucleic acid that is eluted from a suspension of a

hydrophilic matrix or matrix-coated particles or that flows through a column containing a hydrophilic matrix. Accordingly, Su does not describe, suggest, or contemplate critical features of Applicants' claimed process and, therefore, cannot cure the deficiencies of the combination of Mullis and Tasset to make Applicants' invention obvious.

In view of the above comments, Applicants submit that it is clear that Su does not cure the deficiencies of the combination of Mullis and Tasset to provide a case of *prima facie* obviousness to reject Applicants' claimed invention under 35 USC § 103. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection.

The Examiner also relied on the combination of Mullis, Tasset, Su, and also EP Publication No. 0 597 951 A1 ("Raybuck") and US Patent No. 5,869,073 ("Sawan") to reject Claims 1-5, 9-15, 18-22, 24-41, 44-55, and 58-64 as obvious under 35 USC § 103. For the reasons provided below, Applicants respectfully traverse the rejections.

The Examiner relies on Mullis, Tasset, and Su as in the previous rejections. The Examiner further relies on Raybuck because:

> "Raybuck et al. teach at page 5 and the claims, the use of hydrophobic nylon membranes, and hydrophobized membranes in a method of binding nucleic acids on the surface of the membranes with immobilization buffers and washing buffers." (section 17, p. 9 of the Office Action)

The Examiner also relies on Sawan because:

> "Sawan et al. teach at column 7, lines 18-39 and column 9, lines 32-59 the use of hydrophilic and hydrophobic membranes and hydrophilized and hydrophobized membranes, which may be nylon, in the capture and release of nucleic acids from the surface of the membrane." (section 17, p. 9 of the Office Action)

Applicants refer to the previous comments for explaining the various deficiencies of Mullis, Tasset, and Su, alone and in combination, with respect to Applicants' claimed process. In addition, to the extent the Examiner has cited Raybuck and Sawan as teachings of hydrophilic and hydrophobic membranes *per se*, Applicants again note that the inventive feature of Applicants' claimed process does not reside in the hydrophilic, hydrophobic, hydrophilisized, and/or hydrophobisized nature of available membranes; such membranes were known and available to persons of ordinary skill in the art. As explained for Su above, Applicants note that

neither Raybuck nor Sawan, alone or in combination, provide any description of the critical features of Applicants' process to cure the deficiency of Mullis, Tasset, and Su that would be necessary to render Applicants' invention obvious.

Raybuck describes a method of isolating intact nuclei (or other organelles) from eukaryotic cells that relies on the formation of a mat or mesh of DNA released from a small portion of lysed nuclei on a membrane that is able to gently trap and support a large portion of unlysed intact nuclei from eukaryotic cells (see, e.g., p. 5, lines 5-6; Claim 1, of Raybuck). The nuclei may be released by degrading the DNA mesh, e.g., by nuclease digestion, followed by physically manipulating the membrane containing the nuclei and DNA mesh, e.g., by washing or centrifuging the nuclei away from the DNA mesh (see, e.g., p. 5, lines 14-25, of Raybuck). In fact, Raybuck actually teaches how to digest away the DNA mesh and avoid degradation to the intact nuclei and their contents (see, e.g., p. 6, lines 14-18, of Raybuck). Clearly, Raybuck describes a procedure and a goal (isolation of intact nuclei) totally distinct from Applicants' process.

Sawan describes anti-microbial filters produced by coating a filter with a composition comprising a non-metallic, anti-microbial compound, such as a biguanide polymer, and an anti-microbial metal (see, e.g., col. 8, line 6-col. 9, line 7; col. 10, line 65-col. 11, line 26, of Sawan). The filters may be any of a variety of known hydrophobic or hydrophilic membranes (see, col. 7, lines 18-39, of Sawan) or membranes having a combination of hydrophobic and hydrophilic regions (see, col. 9, lines 32-59, of Sawan). The anti-microbial filters of Sawan are particularly useful as components of multi-dose liquid dispensing containers designed to prevent external microbial contamination of the liquid during repeated use (see, e.g., col. 1, lines 63-65; Figures 1-5, of Sawan). Clearly, Sawan does not describe any method for isolating nucleic acids, and provides no teaching or suggestion of Applicants' claimed process.

Alone and together, Raybuck and Sawan fail to advance the combination of Mullis, Tasset, and Su to provide the art with Applicants' claimed process of isolating nucleic acids. Raybuck and Sawan do not even recognize the features or advantages of Applicants' process as discussed above. Raybuck and Sawan only provide documents that mention the existence of hydrophilic and hydrophobic membranes that have been employed over the years in various laboratory and manufacturing procedures.

In view of the above comments, Applicants respectfully submit that the combination of Mullis, Tasset, Su, Raybuck, and Sawan clearly fails to provide a basis to reject Applicants' claims as obvious as required by 35 USC § 103. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection.

The Examiner also rejected Claims 1-5, 9-15, 18-22, 24-41, 44-55, and 58-64 as obvious over the combination of Mullis, Tasset, Su, Raybuck, and Sawan, and further in view of US Patent No. 5,728,531 ("Yamada"). The Examiner applies Mullis, Tasset, Su, Raybuck, and Sawan as in the previous rejections noting:

> "Yamada et al. teach at example 4, the use of membranes, in a method of binding nucleic acid on the surface of the membranes with immobilization buffers and washing buffers.
>
> "It would have been prima facie obvious to one of ordinary skill in the art at the time of filing the instant application to combine the teachings of Mullis, Tasset et al., Su, Raybuck et al., Sawan et al. and Yamada et al. because each of Mullis, Tasset et al., Su, Raybuck et al., Sawan et al. and Yamade et al. teach a process for isolating nucleic acids comprising charging a non-silicious surface with nucleic acid from the top of the surface where the nucleic acid is immobilized on the surface of the filter, using buffers for immobilization and washing. *The teachings of Yamada et al. make obvious the modification of the method by using buffers which contain citric acid in the capture of nucleic acids on the surface of the membrane.*
>
> "One of ordinary skill in the art would have been motivated to combine the teachings of Mullis, Tasset et al., Su, Raybuck et al., Sawan et al. and Yamada et al. because the citric acid buffer taught by Yamada et al. is desirable and beneficial to use in a method of binding nucleic acids to membranes and is a well known and obvious choice which is available to one of ordinary skill in the art for practicing the method. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing [of] the instant claimed invention given the teachings of Mullis, Tasset et al., Su, Raybuck et al., Sawan et al., and Yamada et al." (section 18, pp. 11-12 of the Office Action; emphasis added).

For the reasons provided below, Applicants respectfully traverse the rejection.

Applicants refer to their above comments delineating the deficiencies of Mullis, Tasset, Su, Raybuck, and Sawan, alone and in combination. As noted in the above excerpt from the Office Action, the Examiner relies on Yamada for providing to the Examiner's combination of documents, a description of using citric acid buffers in immobilizing nucleic acids to membranes. Applicants' claimed process may indeed be carried out using an immobilization buffer based on a polyhydroxycarboxylic acid, such as citric acid buffer (see, e.g., in Example 12, p. 30, line 5-p. 31, line 4 (Table 10), of the specification), however, the inventive features of Applicants' claimed process have been explained above and clearly do not rest on the presence of citric acid-based buffers *per se*. Yamada describes gibberellin-labeled DNA probes for *detecting* a target nucleic acid already immobilized on a solid support by a standard hybridization reaction. The hybridization reaction between a gibberellin-labeled DNA and a nucleic acid immobilized on a solid support may be carried out using a citric acid buffer (see, e.g., Example 14, col. 10, lines 37-41, of Yamada). The gibberellin-labeled DNA probes of Yamada that hybridize to a target nucleic acid immobilized on the solid support can then be detected using anti-gibberellin antibody labeled by any of a number of molecules commonly employed for immunodection systems (see, e.g., col. 3, line 58-col. 4, line 17, of Yamada). The hybridization reactions in Yamada involve immersing nylon films containing UV-irradiated (covalently bound) target DNA in a hybridization solution and other solutions to generate a detectable signal on the films (see, Example 14, col. 10, line 27-col. 11, line 20, of Yamada). Clearly, Yamada does not describe a process for isolating nucleic acids according to Applicants' claimed invention: captured DNA of interest is covalently linked to the surface in Yamada and is not eluted.

The above comments show that combining Yamada with the other documents cited by the Examiner still cannot provide the person of ordinary skill in this art with a suggestion of Applicants' claimed process for isolating nucleic acids. Accordingly, the combination of Mullis, Tasset, Su, Raybuck, Sawan, *and* Yamada fails to render Applicants' claims obvious under 35 USC § 103. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

The above amendments, comments, and Exhibit A clearly show that Applicants' claimed invention is fully supported by the specification and that none of the documents cited by the Examiner, alone or in any combination thereof, teaches or suggests Applicants' claimed process for isolating nucleic acids. Accordingly, Applicants submit that the claims, as amended herein, are now in condition for allowance and respectfully request that the Examiner enter the amendments, withdraw the rejections, and pass Claims 1-5, 9-22, 24-41, 44-51, 53-55, 58-64, and 67-75 to allowance.

Respectfully submitted,

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October 21, 2003
Date

Stephanie L. Leicht
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